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Screening the Monoamine Oxidase B Gene in 100 Male Patients With Schizophrenia: A Cluster of Polymorphisms in African-Americans But Lack of Functionally Significant Sequence Changes

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The monoamine oxidase B (MAO-B) gene was examined in 100 alleles derived from 80 Caucasian, 10 African-American, 5 Asian, and 5 Native American male patients with schizophrenia to identify sequence changes that might be associated with the disease. Approximately 235 kb of genomic sequence, primarily in coding regions, were screened by dideoxy fingerprinting, a modification of single-strand conformational polymorphism (SSCP) analysis that detects virtually 100% of sequence changes [Sarkar et al. (1992): Genomics 13:441–443; Liu and Sommer (1994): PCR Methods Appl 4:97–108]. No sequence changes of likely functional significance were identified, suggesting that mutations affecting the structure of the MAO-B protein are uncommon in the general population and are unlikely to contribute significantly to the genetic predisposition to schizophrenia. Eight polymorphisms were identified in African-Americans and Native Americans, but none were identified among Caucasians. Of the eight observed polymorphisms, a set of five transitions and one microdeletion was identified within approximately 17 kb of genomic sequence in the same 3 African-American individuals, while the remaining 7 African-Americans had a sequence identical to that in Caucasians. The presence of two such haplotypes, without intermediates, is compatible with the hypothesis that germline mutations can occur in clusters, as also suggested by other recent findings. *Am. J. Med. Genet. 74:44–49, 1997.*

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INTRODUCTION

Monoamine oxidase A and B (MAO-A, MAO-B) genes metabolize biogenic amines in the central nervous system via oxidative deamination. Located on the outer mitochondrial membrane, MAO-A preferentially oxidizes serotonin, norepinephrine, and epinephrine, while MAO-B preferentially oxidizes phenylethylamine and benzylamine [reviewed in Grimsby et al., 1991]. Dopamine, tyramine, and tryptamine are common substrates for both forms of the enzyme. RNA hybridization (Northern) studies have demonstrated that nearly all human tissues contain mixtures of both forms of the enzyme, with the exceptions of the placenta, where MAO-A predominates, and platelets and lymphocytes, where MAO-B is predominantly expressed [Grimsby et al., 1991]. High levels of MAO-B are found in astrocytes and serotonergic neurons, while high levels of MAO-A are found in catecholaminergic neurons [reviewed in Weyler et al., 1990]. Differential expression of the enzymes occurs during development, with MAO-A activity preceding that of MAO-B. In the adult brain, MAO-B expression is higher. Regulation of enzyme expression appears to be at the transcriptional level [Weyler et al., 1990].

MAO-A and MAO-B are encoded by two separate, but closely linked, genes that have been localized to Xp11.23–Xp22.1. Both genes are approximately 60 kb in size, contain 15 exons, and have identical exon-intron organization. The separate genes are believed to have been derived by duplication of a common ancestral gene. MAO-A and MAO-B are 527 and 520 amino acids, respectively, and share 71% amino-acid identity [Weyler et al., 1990].

MAO activity levels in fibroblasts and platelets have been shown to vary as much as 50-fold between indi-

viduals. Complete loss of activity is compatible with life, as demonstrated in males with submicroscopic deletions in the X chromosomal region containing the MAO genes, as well as in the Norrie disease gene [reviewed in Weyler et al., 1990]. A severe neurological phenotype, including mental retardation and asocial behavior, is evident in such individuals. Recently, the absence of MAO-A activity, caused by a nonsense mutation, cosegregated with mild mental retardation and abnormal, antisocial behavior (e.g., arson, attempted rape) in males from a Dutch pedigree [Brunner et al., 1993a,b]. Although the data often have not been consistent, abnormal MAO-A or MAO-B activity levels have been associated with a number of other psychiatric phenotypes; for example, low MAO-B activity has been associated with alcoholism, schizophrenia, and suicidal behavior [reviewed in Sandler et al., 1981; Wyatt et al., 1980; Fowler et al., 1982; Marcolin and Davis, 1992].

A possible role for the MAO-B gene in schizophrenia was explored herein by examining the gene in 100 male patients with schizophrenia to determine if any sequence changes of likely functional significance could be identified.

MATERIALS AND METHODS

Study Participants

DNA samples were obtained from a large number of patients with schizophrenia (cases), as defined by DSM-III-R criteria and unaffected controls, as previously described [American Psychiatric Association, 1987; Sobell et al., 1993]. Briefly, cases were ascertained primarily through state mental institutions in Minnesota, and diagnoses were made by a research psychiatrist (L.L.H.) based on extensive medical records. Only male patients were utilized.

Laboratory Methods

Human genomic DNA was amplified by the polymerase chain reaction (PCR), as previously described [Liu et al., 1995; Dutton et al., 1993], with oligonucleotide primers as listed in Table I. Dideoxy fingerprinting (ddF) [Sarkar et al., 1992; Liu and Sommer, 1994] was used to screen the majority of the MAO-B gene in overlapping segments of about 150 base pairs each. The ddF method, which combines aspects of dideoxy sequencing and single-strand conformational polymorphism (SSCP) analysis, detects virtually 100% of mutations when performed with optimized conditions [Sarkar et al., 1992; Liu and Sommer, 1994] (specific conditions are available upon request). Samples with abnormal ddF patterns were sequenced by the method of genomic amplification with transcript sequencing (GAWTS), as previously described [Stoflet et al., 1988; Sommer and Vielhaber, 1994].

In the 5′ region and exon 1, due to the high G + C content, bidirectional denaturation fingerprinting was employed instead of ddF and GAWTS [Liu and Sommer, manuscript in preparation]. In this method, cycle sequencing in both the upstream and downstream orientations is performed with one dideoxyribonucleotide. The bidirectional products are combined and electrophoresed on a denaturing gel with either MDE™ (AT Biochem; Malvern, PA) or GeneAmp™ (Applied Biosystems; Foster City, CA) matrix. By repeating the reaction with a second dideoxyribonucleotide, 100% of altered nucleotides can be resolved as either missing or added bands.

RESULTS

A total of 100 male patients diagnosed as schizophrenic according to DSM-III-R criteria was selected for examination of the MAO-B gene. Table II displays selected demographic and disease characteristics for these patients. The putative promoter region, 5′ untranslated region, coding exons, and flanking splice junctions of the MAO-B gene were analyzed for the presence of Variants Affecting Protein Structure or Expression (VAPSEs) [Sobell et al., 1992]. By definition, a sequence change is a VAPSE if it: 1) changes the amino acid structure of the protein (e.g., missense change, nonsense change, or insertion/deletion causing frameshift); 2) interrupts a splice junction consensus sequence; or 3) interrupts a known consensus regulatory sequence. Whether the VAPSE is of likely *functional* significance can be inferred. For example, nonsense changes and interruption of splice junctions will almost always be of potential functional significance. Likewise, if a missense change occurs in an amino acid that is highly conserved over evolutionary time, the change is likely to be deleterious [Bottema et al., 1991]. To access whether VAPSEs of likely functional significance are associated with schizophrenia or other phenotypes, case-control and family studies can be undertaken [Sobell et al., 1992].

In the present analysis, no VAPSEs were found, but eight sequence changes were identified (Table III); four of these were silent changes, and four were polymorphisms in intronic regions that had no effect on splice junction consensus sequences. Six polymorphisms occurred in each of 3 unrelated African-Americans (S308, S321, and S568). The most distal of these polymorphisms was identified as well in a Native American (S485). Native Americans had two additional sequence changes. Thus, no polymorphisms were found in the 80 Caucasian and 5 Asian chromosomes analyzed, while a total of eight polymorphisms were found in 10 African-American and 5 Native-American chromosomes. Five of these polymorphisms were found uniquely in African-Americans, two were found only in Native Americans, and one was found in both African-Americans as well as Native Americans.

The rate of polymorphism was estimated by two standard approaches: 1) calculation of the fraction of all sites at which >1% of alleles differ [H_E]; and 2) calculation of the likelihood that a *diploid* individual will be heterozygous at a particular base [H_N] [Ewens et al., 1981; Cooper and Schmidtke, 1984]. H_{Nave} is the average heterozygosity for biallelic polymorphisms. Thus, H_E does not consider allele frequencies, H_N considers the total number of minor alleles found, but not frequencies, and H_{Nave} considers allele frequencies. Estimated polymorphism rates by race for the MAO-B gene are shown in Table IV, along with data on other X-chromosomal and autosomal genes.

TABLE I. Oligonucleotide Primers

Region: name[a,b]	Sequence	Purpose
1: (T7-23)5′UT(−500)-50D	CAGTGCCTGGTACCTTGAAATCACTCA[c]	PCR
1: 5′UT (−326)-22D	GGGATTCTGGGCGGGACTCT	ddF/seq
1: 5′UT(−286)-14D	TCTCCGCCCAGGCA	ddF/seq
1: 5′UT(−134)-14D	AGGCGCTGGTGCAC	ddF/seq
1: 5′UT(−63)-14U	GTCCTGCCTGCCAG	ddF/seq
1: I1(45)-14U	GTCCGAGCGCGTGA	ddF/seq
1: I1(104)-22U	ACTCCAGGTCAGCCTGCCCACG	ddF/seq
1: (SP6-23)I1(127)-47U	CTGCCGTGCGTGGACAGTCTGGGA[c]	PCR
2: (T7-23)I1(−97)-38D	GTGAGCCAGCATGGA[c]	PCR
2: I1(−51)-16D	TGTCTGGCATCCTTGT	ddF/seq
2: I2(53)-16U	CCCAAACTCAGCTTCA	ddF/seq
2: (SP6-23)I2(111)-39U	CACCCTCTTAGAGTCA[c]	ddF/seq
3: (T7-23)I2(−108)-41D	GCTGTATCTATAACTTGT[c]	PCR
3: I2(−83)-17D	CGATTTGCTTATTTCAG	ddF/seq
3: I3(57)-18U	TGTAAGGAAACATCATAG	ddF/seq
3: (SP6-23)I3(111)-40D	ATTTGCATCATCCAGAG[c]	PCR
4: (T7-23)I3(−145)-39D	AGGACACAAGGAGCTA[c]	PCR
4: I3(−47)-20D	TACATTGTAGTAAATATTTC	ddF/seq
4: I4(53)-19U	AAGGATGAAACTTATTACA	ddF/seq
4: (SP6-23)I4(98)-39U	TCACAATGTGCTAGGT[c]	PCR
5: (T7-23)I4(−202)-40D	AGCTACATAGACAGCAT[c]	PCR
5: I4(−41)-18D	TTACATTTGTCTTTCTCC	ddF/seq
5: I5(44)-17U	AAGGATGGTCACAGTAA	ddF/seq
5: (SP6-23)I5(98)-40U	ACAAAGCAGCTACTTGT[c]	PCR
6: (T7-23)I5(−119)-40D	TGACCTTACCACATTGT[c]	PCR
6: I5(−47)-15D	CTGCTCTCCTGCGTT	ddF/seq
6: I6(53)-17U	TCATTTCAGTAGCAGTG	ddF/seq
6: (SP6-23)I6(156)-39U	CAGACTGCCTTACAAG[c]	PCR
7: (T7-23)I6(100)-40D	TGTTAGACATCTCAGAG[c]	PCR
7: I6(−41)-16D	CCATTCCTGCGTTTCT	ddF/seq
7: I7(54)-16U	GTATGCCAGGAAACTG	ddF/seq
7: (SP6-23)I7(86)-40U	ATCACTCTGGAGTTCTA[c]	PCR
8: (T7-23)I7(−33)-41D	CAACAATGTTTAACCATG[c]	PCR
8: I7(−15)-17D	TTGCTTTTCTTTCAGGC	ddF/seq
8: E8(150)-17U	CCAGAAAGGCTCTTTAT	ddF/seq
8: (SP6-23)I8(6)-39U	ACTCACCCTTTTTCCT[c]	PCR
9: (T7-23)I8(−123)-41D	TTGGAGTATAACATGCTT[c]	PCR
9: I8(−71)-18D	GCACTTCATTATATCTGT	ddF/seq
9: I9(50)-18U	TTATCTTGTCAACACTGA	ddF/seq
9: (SP6-23)I9(203)-39U	TCTGCTTCCTACCTAG[c]	PCR
10: (T7-23)I9(−80)-39D	GGCACATGTGTAGCTA[c]	PCR
10: I9(−54)-16D	GCTAGGATGAACCAAC	ddF/seq
10: I10(102)-15U	GCAGGCACTAGGTAG	ddF/seq
10: (SP6-23)I10(172)-38U	ACACGTAGCACTGGC[c]	PCR
11: (T7-23)I10(158)-38D	GCCAGTGCTACGTGT[c]	PCR
11: I10(−47)-16D	CCTCCCTTCTTTCCTT	ddF/seq
11: I11(70)-16U	ATCCCTGCTAGTCACT	ddF/seq
11: (SP6-23)I11(102)-39U	CATGAACTTCAGGACC[c]	PCR
12: (T7-23)I11(−131)-40D	TCAGGATAATGCAACTC[c]	PCR
12: I11(−44)-16D	CTTTCTCTGAGTCTCC	ddF/seq
12: I12(35)-17U	GGATTTCTGTAACAGCT	ddF/seq
12: (SP6-23)I12(39)-39U	GCAGGGATTTCTGTAA[c]	PCR
13: (T7-23)I12(−92)-38D	CTGTGGAAGCTGACC[c]	PCR
13: I12(−41)-16D	TCTGAGACTGACCACT	ddF/seq
13: I13(48)-15U	GGACCTAGAGTTGCC	ddF/seq
13: (SP6-23)I13(80)-39U	CAGGCTCTCAGATATC[c]	PCR
14: (T7-23)I13(−102)-41D	TTGATGGATATCTCAAGA[c]	PCR
14: I13(−49)-16D	GAAAGATGGTGTCGCT	ddF/seq
14: I14(72)-17U	AAGTGTGCTCTTCTTGA	ddF/seq
14: (SP6-23)I14(111)-41U	TTAGTTGAATCACTTAGG[c]	PCR
15: (T7-23)I14(−84)-39D	TGTTCAGAGAGCTGGA[c]	PCR
15: I14(−49)-17D	AATAAAGTGCACAAGCC	ddF/seq
15: 3′UT(45)-18U	CCAAATACAGTAAGAAGA	ddF/seq
15: 3′UT(204)-15U	GCTAAGCCAGGTAAG	ddF/seq
15: (SP6-23)3′UT(317)-39U	TTCATCCTGTGCATGG[c]	PCR

[a] Oligonucleotide numbering system for exonic sequence based on Bach et al. [1988]. Unpublished intronic sequence was kindly provided by Dr. Jean Shih.

[b] Nomenclature according to Sarkar et al. [1990]. Oligonucleotide primer full names reflect the gene (MAO-B), species (HS, homo sapiens), phage promoter sequence at the 5′ end, if any (T7-23 or SP6-23), gene region (I, intron; E, exon), starting basepair (numbering according to Bach et al. [1988], primer length, and orientation of the primer (D, downstream; U, upstream). For example, the oligonucleotide [(T7-23)5′UT(−500)-50D] has a 23-bp T7 phage promoter and begins at bp −500 in the 5′ untranslated region. It is 50 bp in length (including the 23 bp T7 sequence) and is oriented downstream.

[c] T7-23 is a 23-base pair phage T7 promoter region added to the corresponding primer's 5′ end for initiation of transcription by T7 RNA polymerase after PCR. Its sequence is $^{5'}$TAATACGACTCACTATAGGGAGA$^{3'}$. SP6-23 is a 23-base pair phage SP6 promoter region added to the corresponding primer's 5′ end for initiation of transcription by SP6 RNA polymerase after PCR. Its sequence is $^{5'}$ATTTAGGTGACACTATAGAATAG$^{3'}$.

TABLE II. Distribution of 100 Male Patients With Schizophrenia by Race and Disease Indices

Variable	Number (%) or mean (range)
Race	
Caucasian[a]	80 (80%)
African-American	10 (10%)
Asian	5 (5%)
Native American	5 (5%)
Average age at first psychiatric hospitalization (N = 95)	21.5 (9–42)
Average age at onset of schizophrenia (N = 81)[b]	26.0 (15–48)
Average number of hospitalizations (N = 98)	8.0 (1–27)
Average total years of hospitalization (N = 98)	7.3 (1–31)

[a] Caucasians of predominantly Western European descent.
[b] DSM-III-R criteria [American Psychiatric Association, 1987].

DISCUSSION

In this examination of the MAO-B gene in 100 male patients with schizophrenia, no sequence changes of likely functional significance were identified. The sample size was sufficiently large to detect at least one deleterious sequence change with 90% power, even if the attributable risk was only 5% [Schaid and Sommer, 1993].

Of the eight identified sequence changes, a set of five transitions and one microdeletion was identified within approximately 17 kb of genomic sequence in the same 3 African-American individuals, while the remaining 7 African-Americans had a sequence identical to that in Caucasians. The presence of two such haplotypes, without intermediates, is compatible with the hypothesis that germline mutations can occur in clusters, as also suggested by other recent findings in humans and mice. In an evaluation of mutations in the factor IX gene (chromosome Xq27), Ketterling et al. [1995] reported on a family in which two deletions separated by a sense strand insertion had occurred. Both deletions were traced to the germline of the unaffected maternal grandfather [Ketterling et al., 1995]. In another family, two novel point mutations were identified in the hemophiliac proband. Through haplotype, mutational, and paternity analyses, both mutations were traced to the germline of the unaffected maternal grandfather [Ketterling et al., submitted]. The probability of observing even one independently occurring second mutation was estimated to be quite low ($P < .005$), given a germline mutation rate in humans of 3×10^{-10}/bp/generation and the number of base pairs analyzed in the factor IX gene (ibid.). In addition, clustered somatic mutations were also found in brain and liver cells, as assayed by the Big Blue transgenic mouse mutation system [Ketterling et al., manuscript in preparation], a recently developed powerful tool for measuring mutation rate and spectrum in any desired tissue. If clustered mutations do occur, this phenomenon could provide an explanation for the repeated observation that the average rate of polymorphism on the human X chromosome is 3–5-fold lower than on autosomes.

In the present study, the focus was on the coding regions of the MAO-B gene. The promoter region of the gene has been identified [Zhu et al., 1992]. Two Sp1 binding clusters have been observed. These Sp1 sites and a CACCC motif lie within approximately 450 bp upstream of the ATG initiation codon and were found to have positive regulatory effects on MAO-B expression. Within this same region, other transcription factor binding sites were found, including three more potential Sp1 binding sites, three more CACCC sequences, and two CCAAT boxes. Beyond bp −450, only three known transcription factors were identified in the kilobases of DNA examined [Zhu et al., 1992]. In our examination of the MAO-B gene, the majority of sequence in this region (downstream from bp −450) would have been covered. Additionally, while it may be possible that mutations in other regulatory regions were missed and might be related to schizophrenia, analyses of inborn errors of metabolism indicate that the overwhelming majority of disease-causing mutations in most genes will be found in the coding sequence and flanking splice junctions [Scriver et al., 1995]. For example, in 290 consecutive patients with hemophilia B, 97% had the causative mutation identified in exons or splice junction sequences [Gostout et al., 1993]. In cystic fibrosis, 70% of the dis-

TABLE III. Sequence Changes Identified in the MAO-B Gene of 100 Male Patients With Schizophrenia

Nucleotide change	Region (base pair)[a]	Amino acid	Frequency of polymorphic allele by race[b]	Subjects
A→G	Exon 6 (130)	T202T	African-American: .30	S308, S321, S568
C→T	Intron 6 (−15)	I6 (3′)	African-American: .30	Same as above
A→G	Exon 10 (28)	K351K	African-American: .30	Same as above
del C	Intron 10[c]	I10 (5′)	African-American: .30	Same as above
T→C	Intron 10 (−52)	I10 (3′)	African-American: .30	Same as above
T→C	Intron 14 (−3)	I14 (3′)	African-American: .30	Same as above
			Native-American: .20	S485
C→T	Exon 15 (51)	P487P	Native-American: .20	S485
A→G	Exon 5 (18)	P134P	Native-American: .20	S499

[a] Numbering system based on Bach et al. [1988], with the first nucleotide of each exon numbered consecutively from 1. Intronic sequence is positively numbered downstream of the 3′ end of its exons, and negatively numbered upstream of the 5′ region of the next exon.
[b] African-American alleles, 10; Native-American alleles, 5.
[c] The deletion occurs in a group of seven consecutive C nucleotides beginning at bp 42.

TABLE IV. Estimates of Rate of Polymorphism for Selected Autosomal and X-Linked Genes by Race

		Number of Chromosomes Examined		H_E[a]		H_N[a]		H_{Nave}[a]	
	Gene[b]	Caucasian[c]	African-American	Caucasian	African-American	Caucasian	African-American	Caucasian	African-American
X-chromosome	MAO-B	80	10	0	23	0	13.8	0	9.66
	Dystrophin	85	19	39.7	66	48	46		
	Alu (FIX)(five sequences)			7.1		4.5		2.8	
Autosomes	DRD5	120	16	13.2	19.9	7.8	14.9	5.91	7.15
	DRD1	212	22	14.3	7.41	0.14	0.34	3.97	1.74

[a] See text and references for description of $H_{E,N,Nave}$. All rates are $\times 10^{-4}$.
[b] MAO-B, monoamine oxidase B; FIX, factor 9; DRD5, D5 dopamine receptor; DRD1, D1 dopamine receptor.
[c] Caucasians of Western European descent.

ease is caused by a 3-bp deletion removing amino acid 508; however, at least 230 other mutations have been identified which are probably associated with disease [Tsui, 1992]. All of these mutations occur in the coding region or splice junctions [Tsui, 1992].

We conclude that mutations in the MAO-B gene are unlikely to be associated with a significant proportion of schizophrenia. Data from this analysis further suggest the occurrence of clustered mutations among individuals of African-American descent. Additional studies to determine if this phenomenon is more general, and to determine its prevalence and to define possible mechanisms, are indicated.

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